DETAILED ACTION

Application Status

1. In response to the previous Office action, a Non-Final rejection (mailed on 01/14/2009), Applicants filed a response and amendment received on 04/14/2009.

Said amendment amended Claims 1, 4-6, 29 and 31-33; added new Claims 34-35. Claims 2-3, 26 and 30 have been canceled. Claims 1, 4-25, 27-29 and 31-35 are pending.

Examiner's amendment to the Claims

2. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment shown below was given in a telephone interview with Mark Sweet on Nov. 3, 2009.

Amend the claims filed on 04/14/2009 as follows:

1. A method of identifying, screening, characterizing or designing a chemical entity that potentially binds a FIH (Factor Inhibiting HIF (Hypoxia Inducible Factor)), comprising:
(a) generating a three-dimensional model of FIH on a computer wherein the three-dimensional model has the x-ray structural coordinates as set forth in the structure 1, 2 or 3 in Table 3;
(b) providing a structural model of a chemical entity on the computer;

(c) identifying the amino acid residues forming a binding site of the FIH from the three-dimensional model in step (a) in order to generate a three-dimensional representation of the binding site of the FIH, wherein the binding site of the FIH comprises amino acids Tyr145, Leu186, Leu188, Thr196, Phe207, Lys214 and Ile281 as set forth in SEQ ID NO: 30, wherein the amino acids have the structural coordinates as shown in the structure 1, 2 or 3 in Table 3;
(d) employing the structural model from step (b) and the three-dimensional representation from step (c) to identify a chemical entity that potentially binds with the binding site of the FIH; and
(e) obtaining the chemical entity.

4. Canceled.

5. The method according to claim 1, wherein said chemical entity is predicted to form hydrophobic interactions with the side chain of one or more amino acid residues selected from Leu186, Leu188, Thr196, Phe207, and Ile281 according to SEQ ID NO: 30.

6. The method according to claim 1, further comprising:
(f) contacting the chemical entity with a polypeptide comprising SEQ ID NO:33 and a polypeptide comprising SEQ ID NO:30; and
(g) monitoring for hydroxylation of said polypeptide comprising SEQ ID NO: 33 to identify a potential inhibitor of hydroxylation.

7-25 and 27-28. Canceled.

29. A method of identifying, screening, characterizing or designing a chemical entity that is potentially capable of inhibiting hydroxylation of a β-carbon of an asparagine of an HIF polypeptide by a FIH polypeptide, comprising:

(a) generating a three-dimensional model of FIH on a computer wherein the three-dimensional model has the x-ray structural coordinates as set forth in the structure 1, 2 or 3 in Table 3;

(b) providing a structural model of a chemical entity on the computer;

(c) identifying the amino acid residues forming a binding site of the FIH from the three-dimensional model in step (a) in order to generate a three-dimensional representation of the binding site of the FIH, wherein the binding site of the FIH comprises amino acids Tyr145, Leu186, Leu188, Thr196, Phe207, Lys214 and Ile281 as set forth in SEQ ID NO: 30, wherein the amino acids have the structural coordinates as shown in the structure 1, 2 or 3 in Table 3;

(d) employing the structural model from step (b) and the three-dimensional representation from step (c) to identify a chemical entity that is potentially capable of inhibiting hydroxylation by the FIH polypeptide of the β-carbon of the asparagine 18 according to SEQ ID NO: 31, or the asparagine 29 according to SEQ ID NO: 32; and

(e) obtaining the chemical entity.

31. Canceled.

32. The method according to claim 29, wherein said chemical entity is predicted to form hydrophobic interactions with the side chain of one or more amino acid residues selected from

Leu186, Leu188, Thr196, Phe207, and Ile281 as set forth in SEQ ID NO: 30.

33. The method according to claim 29, further comprising:
(f) contacting the chemical entity with a polypeptide comprising SEQ ID NO:33 and a polypeptide comprising SEQ ID NO:30; and
(g) monitoring for hydroxylation of said polypeptide comprising SEQ ID NO: 33 to identify a potential inhibitor of hydroxylation.

34. The method according to claim 1, wherein said chemical entity is predicted to form electrostatic or hydrogen bonding interactions with one or more amino acid residues selected from Tyr145, Thr196, and Lys214 according to SEQ ID NO: 30.

35. The method according to claim 29, wherein said chemical entity is predicted to form electrostatic or hydrogen bonding interactions with one or more amino acid residues selected from Tyr145, Thr196, and Lys214 according to SEQ ID NO: 30.

Statement of Reasons for Allowance

3. Claims 1, 5, 6, 29 and 32-35 are allowed. The following is an examiner's statement of reasons for allowance:

The instant invention is drawn to a novel and unobvious method of identifying, screening, characterizing or designing a chemical entity that potentially binds a FIH which has an aspartate hydroxylase activity to hypoxia-inducible factor (HIF). FIH

polypeptide catalyzes β-hydroxylation of HIF Asn803, which blocks interaction with the transcriptional co-activator p300. The inhibition of HIF hydroxylases strongly activates the HIF transcriptional cascade; and inhibition of the FIH results in a pro-angiogenic response that may be used in the treatment of cardiovasculare diseases/ischaemic hypoxic vascular disseases (see instant specification, top of page 2). However, it is known that human cells contain other enzymes belonging to the same family as the HIF hydroxylases (specification at p. 2, top). Thus, the claimed method is useful for identifying a potential chemical entity that is specific for HIF hydroxylase and is useful as a therapeutic agent, for example.

In view of the instant examiner's amendment to the claims, all outstanding objections and rejections are withdrawn.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance.

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 10AM-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/David J. Steadman/
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